PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	06.02.2006
Applicant's or agent's file reference P1025PC00	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/ES2004/000572	21.12.2004	22.12.2003

Applicant
RAGACTIVES, S.L. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Roche, S Tel. +49 89 2399-8031

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P1025PC00	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/ES2004/000572	International filing date *(day/month/year)* 21.12.2004	Priority date *(day/month/year)* 22.12.2003
International Patent Classification (IPC) or both national classification and IPC C07C215/54		
Applicant RAGACTIVES, S.L. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21.10.2005	06.02.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Breimaier, W Telephone No. +49 89 2399-8327

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/ES2004/000572

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-18 as published

Claims, Numbers

1-14 received on 25.10.2005 with letter of 21.10.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1 : Organic Process Research & Development, 2002, vol. 6, pp. 379-383
D2 : US-A 5382600 ✓
D3 : WO 01/49649
D4 : WO 98/29402 (ES 2186018)

novelty (Art. 33(2) PCT)
The subject-matter according to claims 1 to 14 is novel.

The present application according to claims 1 to 11 concerns a method for making known tolterodine of formula (I) which mainly differs from the available state of the art processes that the hydroxyl-protected aldehyde of formula (II) rather than the free aldehyde (see D1, scheme 1, 3a; D3, claims 1-4; D4, examples 2 and 3) is used.
The intermediates (II) and (III), in particular, (II) according to claims 12 and 13 differs from D1 in the protective moiety "R" (cf scheme 2, 3b) and the hydrobromide salt of the propylamine (III) according to claim 14 is not explicitly mentioned in D2 (cf column 2, lines 32-37 and column 14, lines 2-3).

inventive step (Art. 33(3) PCT)
The subject-matter according to claims 1 to 14 is inventive.

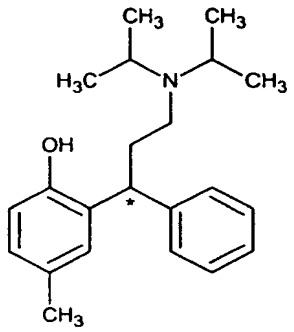
In view of the closest state of the art D1 wherein the free aldehyde 3a which is made by the rhodium catalysed hydroformylation of the phenylethene 2a is subjected to reductive amination furnishing tolterodine in an overall yield up to 60% (see scheme 1 and table 1), the problem posed is the provision of an alternative method for making tolterodine (I) in good yields.
This is solved by subjecting the hydroxyl-protected aldehyde (II) which is obtainable by oxidation of the hydroxyl-protected alcohol (IV) to reductive amination furnishing the hydroxyl-protected diisopropylamine (III) (see examples 4 and 5).
In the known processes the free aldehyde is subjected to reductive amination. Thus, the skilled person would not have been motivated to the use of the hydroxyl-protected reactants requiring additional protection-deprotection steps. Surprisingly, tolteridone is obtained in an easy manner and in good yields.
The intermediates (II) and (III) are inventive in view of the overall inventive process.

further remarks

- Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D4 is not mentioned in the description, nor are these documents identified therein.
- The description is not exactly adapted to the claims.

CLAIMS (AMENDMENTS UNDER Art. 34)

1. A process for obtaining 3-(2-hydroxy-5-methylphenyl)-N,N-diisopropyl-3-phenylpropylamine of formula (I)



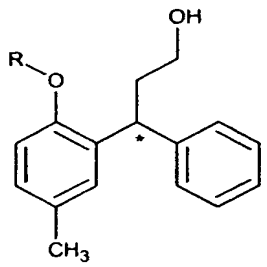
(I)

wherein the asterisk indicates an asymmetric carbon atom,

its enantiomers or mixtures thereof, or its pharmaceutically acceptable salts,

comprising:

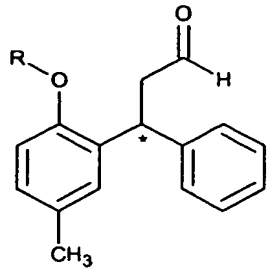
(a) oxidizing the alcohol of formula (IV)



(IV)

wherein the asterisk has the previously indicated meaning and R is a hydroxyl protecting group,

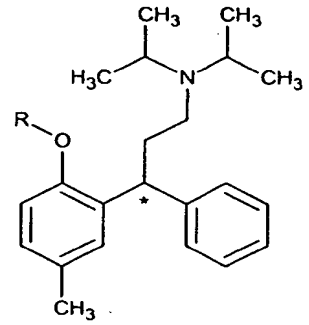
to give a compound of formula (II)



(II)

wherein R and the asterisk have the previously indicated meanings;

(b) reacting the compound of formula (II) with diisopropylamine in the presence of a reducing agent to give a compound of formula (III)



(III)

wherein R and the asterisk have the previously indicated meanings;

(c) removing the hydroxyl protecting group from the compound of formula (III) to obtain the compound of formula (I); and

(d) if so desired, separating the desired (R) or (S) enantiomer, or the mixture of enantiomers, and/or converting the compound of formula (I) into a pharmaceutically acceptable salt thereof.

2. A process according to claim 1, wherein said reducing agent is selected from $NaBCNH_3$, $NaB(AcO)_3H$ and hydrogen in the presence of Pd/C.

3. A process according to claim 1, wherein the reaction of the compound of formula (II) with diisopropylamine is carried out in a solvent selected from tetrahydrofuran, dichloromethane, acetonitrile and methanol.

4. A process according to claim 1, further comprising converting said compound of formula (III) into a salt, and, if desired, isolating said salt from the compound of formula (III) before removing the hydroxyl protecting group [step (c)].

5. A process according to claim 4, wherein said salt of the compound of formula (III) is an inorganic acid addition salt, preferably the hydrochloride, hydrobromide or sulfate of the compound of formula (III).

6. A process according to claim 4 or 5, wherein said salt of the compound of formula (III) is N,N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine hydrobromide.

7. A process according to claim 1 or 4, wherein the removal of the hydroxyl protecting group from the compound of formula (III), or from said salt of the compound of formula (III), is carried out by means of treating with a mineral acid, a Lewis acid or an organic sulfide.

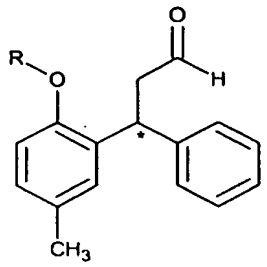
8. A process according to claim 7, wherein the removal of the hydroxyl protecting group from the compound of formula (III), or from said salt of the compound of formula (III), is carried out by means of treating with aqueous hydrobromic acid in acetic acid.

9. A process according to claim 1, wherein the obtained compound of formula (I) is selected from the (R) enantiomer, the (S) enantiomer and their mixtures.

10. A process according to claim 1, wherein the separation of the (R) or (S) enantiomers from the compound of formula (I) is carried out by means of fractional crystallization of the salts of said enantiomers with chiral acids.

11. A process according to claim 1, wherein the oxidation of the alcohol of formula (IV) to obtain the aldehyde of formula (II) is carried out using pyridinium chlorochromate (PCC), SO_3.pyridine (SO_3.pyr), the 2,2,6,6-tetramethylpiperidine (TMPP) N-oxide/NaClO system, or the Swern method.

12. A compound of formula (II)



(II)

wherein

R is a C_1-C_4 alkyl group, an optionally substituted benzyl group, aralkyl, silyl ether, carbonate or benzyl ester; and

the asterisk indicates an asymmetric carbon atom.

13. A compound according to claim 12, wherein R is methyl.

14. N,N-diisopropyl-3-(2-metoxi-5-methylphenyl)-3-phenylpropylamine hydrobromide.